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The use of levetiracetam in refractory status epilepticus

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Summary Six patients with status epilepticus (SE) of various etiologies refractory to at least two antiepileptic drugs (AEDs) had complete cessation of their seizures following administration of oral levetiracetam (LEV). Seizure types included convulsive, focal, and nonconvulsive status epilepticus. Effective doses of levetiracetam ranged from 500 to 3000 mg/day, achieving seizure control within 12–96 h. No significant adverse events were noted. Adjunctive levetiracetam should be considered for patients with status epilepticus unresponsive to initial therapy.

Introduction

Despite significant advances in the treatment of epilepsy, status epilepticus (SE) continues to be a medical emergency affecting more than 100,000 individuals each year with a mortality >20%.[1] Several protocols for the treatment of status epilepticus are in general use.[2] Refractory status epilepticus, defined as seizures lasting longer than 60 min despite treatment with a benzodiazepine and adequate loading dose of an intravenous antiepileptic drug (AED)[3] affects 6000–20,000 people per year in the US and portends a mortality ranging from 32 to 77%.[4] Refractory status epilepticus is associated with more frequent medical complications, longer hospitalizations and duration of intensive care, and increased functional disability compared to patients who responded to the first AED after an initial benzodiazepine.[3] Risk factors for

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Table 1 Status epilepticus case summaries

Case	Age	Sex	Seizure type	Cotherapy	SE duration	SE etiology	Maximum LEV dose used to treat SE (mg/day)	Time to LEV response
1.	57	F	Convulsive, focal	PHT, LZP, VPA, CBZ, PB	24 Days	Left insular vascular lesion	3000	4 Days
2.	91	M	Right focal	PHT, VPA	9 Days	Left MCA infarct	3000	2 Days
3.	63	F	Right focal	PHT, VPA	7 Days	Left frontal hemorrhagic infarct	2000	2 Days
4.	16	F	Convulsive and nonconvulsive	LZP, PB, TPM	2 Days	Static encephalopathy	500	1 Day
5.	34	M	Partial motor with and without secondary generalization	LZP, PB, VPA, LTG	3 Days	Posttraumatic epilepsy	3000	12 h
6.	25	F	Convulsive and nonconvulsive	LZP, MDZ, VPA, CBZ	9 Days	Noncompliance	1000	36 h

CBZ, carbamazepine; GBP, gabapentin; ICH, intracerebral hemorrhage; LEV, levetiracetam; LTG, lamotrigine; LZP, lorazepam; MDZ, midazolam; PB, phenobarbital; PHT, phenytoin; SE, status epilepticus; TPM, topiramate; VPA, valproic acid.

refractory status epilepticus include nonconvulsive status epilepticus, and focal motor seizures.[3] Outcome is closely linked to the etiology of status epilepticus.[5]

Current recommendations for the treatment of refractory status epilepticus include midazolam (MDZ), pentobarbital, and propofol.[1] Respiratory depression and/or hypotension may result from treatment,[1] which may necessitate endotracheal intubation and/or vasosuppressor support.[6] Although individual preferences regarding therapeutic protocols vary, neurologists agree that treatment should be started early to prevent brain injury secondary to sustained status epilepticus.[6] Visible evidence of such injury has recently been documented on MRI.[7] Despite weeks or months of high dose suppressive therapy in an effort to control refractory status epilepticus, outcomes may not prove satisfactory.[5] Randomized controlled trials comparing treatments of refractory status epilepticus have not yet been performed.[3]

We present six cases of patients with status epilepticus that persisted despite initial AED therapy, but ultimately responded to treatment with levetiracetam (LEV), a new AED. In 1999, LEV received FDA approval as adjunctive therapy for the treatment of partial onset seizures in adults with epilepsy.[8] Preliminary observations suggest that LEV may be effective in generalized seizures as well.[9] LEV has a unique pharmacologic profile; it is not metabolized by the liver, has no known drug—drug interactions, has low protein binding (<10%), is renally excreted, the extent of absorption is not affected by food, and has a half life of 6—8 h in adults.[10] At the time these patients were treated, only oral tablets (250, 500, 750 mg doses) were available. However, an oral solution (100 mg/ml) received FDA approval in July, 2003. An intravenous formulation is under development (personal communication).

Four of these six patients fit the strict definition of refractory status epilepticus stated above. The other two (Cases #2 and #3) do not, because they did not receive an initial benzodiazepine. However, these two cases are included because they were 'refractory' in a clinical if not technical sense, as they each failed both phenytoin (PHT) and valproate therapy.

Case histories

Case 1. A 57-year-old woman with a 30-year history of epilepsy had right-sided focal seizures with secondary generalization at home. Her phenytoin level was 'therapeutic' at 16.5 μg/ml upon arrival to the emergency room. After treatment with intravenous lorazepam (LZP) and valproic acid (VPA), the clinical seizures stopped, focal seizures occurred intermittently. The patient did not wake up. EEG demonstrated left temporal PLEDS. MRI revealed a left insular lesion of uncertain age, thought to be vascular. Valproic acid level increased from 57 to 79 μg/ml over the next 24 h. Phenytoin remained at 15 μg/ml. Carbamazepine (CBZ) was begun at 200 mg Q 8 h. Right-sided focal seizures continued and the patient became less responsive. Ammonia was 113 μg/dl. By hospital day 18, the patient remained unresponsive; phenytoin level was

14 μg/ml, valproic acid 91 μg/ml, and carbamazepine 5 μg/ml. Ammonia had increased to 270 μg/dl. Phenobarbital (PB) had been added and the level was 20 μg/ml. On hospital day 19, LEV 1000 mg tablets were crushed and administered via NG tube Q 8 h. Valproic acid and phenytoin were discontinued. On hospital day 22, ammonia had decreased to 37 μg/dl. The patient was receiving phenobarbital 120 mg/day and her level was 35 μg/ml. LEV dose was still 3000 mg/day. Seizures stopped on hospital day 24, 4 days after adding LEV. By hospital day 27, the patient was alert and oriented. She was discharged on phenobarbital and LEV. Later the phenobarbital was discontinued, and she remains well controlled on LEV 2500 mg/day.

Case 2. A 91-year-old man with a history of atrial fibrillation, hypertension, and TIAs presented with garbled speech and right-sided facial twitching. He had been prescribed phenytoin for questionable seizures in the past, but had not taken it for several years. CAT scan revealed a left MCA infarct. Because of episodes of altered consciousness thought to be seizures, he was started on phenytoin. Despite a therapeutic phenytoin level, the patient had right-sided focal motor seizures and was loaded with intravenous valproic acid, achieving a level of 95 μg/ml within 24 h. The patient became unresponsive with shallow, irregular breathing and intermittent right-sided seizures. EEG revealed left-sided PLEDS. On hospital day 7, the patient continued to have seizures despite valproic acid levels of 113 μg/ml and phenytoin of 13.6 μg/ml. Consequently, crushed LEV tablets were added via NG tube at 1000 mg TID. Two days later, the patient's EEG was improved and it appeared that his seizures were controlled. His phenytoin was discontinued. On hospital day 11, his valproic acid was also discontinued. The patient's level of consciousness gradually improved, and his EEG suggested a postictal state. On hospital day 12, the patient was on LEV monotherapy 3000 mg/day. By the next day, he was awake, alert, and had only some mild expressive language problems. The patient was discharged to the rehabilitation unit and within a month was discharged home on LEV 2500 mg/day. He had no residual right-sided weakness, and only minimal dysphasia. Two months later he had an intracranial hemorrhage into the region of his infarct while on coumadin and expired.

Case 3. A 63-year-old woman was admitted with right-sided seizures, altered mental status and slurred speech. CAT scan showed a left frontal lesion, possibly a hemorrhagic infarct. She was loaded with fosphenytoin and given additional doses of phenytoin, but continued to have seizures after 24 h despite phenytoin levels of 15—20 μg/ml. Intravenous valproic acid was added, followed by maintenance valproic acid therapy. On hospital day 2, her phenytoin level was 10 μg/ml and her valproic acid level was 84 μg/ml. She continued with focal seizures and fluctuating levels of consciousness. EEG revealed left frontal PLEDS. On hospital day 5, she continued to have intermittent right focal seizures and was only intermittently arousable. Phenytoin level was 14 μg/ml and valproic acid level was 94 μg/ml. LEV was added (500 mg BID) via NG tube and increased to 500 mg QID over the next 24—48 h. Two days later, on hospital day 7, she was able to look around the room and had no more seizures. EEG showed resolution of her seizure focus. Phenytoin level was 15 μg/ml, valproic acid level 61 μg/ml, and she continued LEV at 500 mg BID. By hospital day 10, she was fully alert. Phenytoin was discontinued. Valproic acid was continued at 500 mg BID. LEV was decreased to 1500 mg/day. After further consultation and an MRI, the discharge diagnosis was lupus cerebritis with CNS vasculitis and coagulopathy. The patient was discharged to the rehabilitation institute on valproic acid, LEV, and coumadin.

Case 4. A 16-year-old girl with seizures since age 6 years, static encephalopathy, Dandy—Walker syndrome and shunted hydrocephalus had failed treatment with carbamazepine, clonazepam, phenytoin, and valproic acid and was maintained on phenobarbital and topiramate (TPM). Elective spinal fusion surgery was followed by 3—4 partial complex seizures with secondary generalization. After treatment with intravenous lorazepam and additional phenobarbital (level increased from 25.6 to 33.9 μg/ml), the patient's seizures appeared to be controlled. However, the next day she was unarousable. EEG revealed brief runs of generalized spikes and waves every 30—40 s consistent with nonconvulsive status epilepticus. Because the patient had not tolerated phenytoin or valproate in the past and was allergic to carbamazepine, she was given 500 mg of LEV (28 mg/kg), crushed and dissolved in water and administered via NG tube. The following day, the patient woke up and the EEG did not reveal any seizure activity. The patient continued on 250 mg BID of oral LEV in addition to phenobarbital 60 mg BID and topiramate 50 mg BID.

Case 5. A 34-year-old man with a history of post-traumatic epilepsy was admitted with simple partial seizures of the right arm and leg with and without secondary generalization after noncompliance with phenobarbital 100 mg/day (admission level 0) and alcohol abuse. On initial examination, the patient

was confused but able to follow simple commands. He had mild (4/5) left arm and leg weakness and a left-sided Babinski sign. Seizures did not respond to lorazepam or loading doses of phenobarbital or valproic acid (Depacon 3 g), and patient was intubated. (The patient did not receive phenytoin due to a phenytoin allergy.) Chest X-ray revealed aspiration pneumonia with a large pleural effusion that required thoracentesis. Head CT revealed bifrontal encephalomalacia and evidence of previous craniotomy and facial bone repair. Initial EEG demonstrated bifrontal polyspike wave discharges at 3—4 Hz lasting approximately 15 s and recurrent spikes in the left frontal head region. EEG on day 2 revealed electrographic seizures with onset in the left frontal region extending into the right frontal region lasting 30—50 s. Patient received a phenobarbital infusion of 15 mg/h and additional valproic acid (Depacon 1 g Q 4 h). On day 3, lamotrigine (LTG) was begun at 100 mg Q 8 h, together with LEV 1 g Q 8 h administered as crushed tablets via NG tube. The patient also received intravenous rocephin and multivitamins. The next day, after approximately 12 h of receiving lamotrigine and LEV, the patient had no more clinical seizures. The EEG still had some residual spikes, but the electrographic seizures had resolved. By the next day, the EEG revealed only diffuse slowing. The patient remained in hospital for 27 days. At the time of discharge, he had mild right-sided weakness. He was discharged home on lamotrigine 100 mg BID, divalproex sodium 1 g every 8 h, and LEV 1 g BID.

Case 6. A 25-year-old woman with mild mental retardation and seizures since the age of 5 years had a left temporal lobectomy at age 12 years. Between the age 12 and 25 years she continued to have infrequent seizures despite multiple AED adjustments. While taking carbamazepine and valproate, the patient was admitted with convulsive status epilepticus, likely related to medication noncompliance (carbamazepine level 3.2 μg/ml, divalproex sodium 21 μg/ml). She was treated with intravenous lorazepam, midazolam, and valproate sodium, which stopped the convulsions after approximately 8 h. For the following 3 days, she remained poorly responsive with a waxing and waning mental status, originally attributed to the benzodiazepine treatment. However, after cessation of the benzodiazepines, there was no improvement in mental status and the patient was admitted to the epilepsy monitoring unit. Over the next 24 h, 30—40 electrographic seizures were noted and the patient was diagnosed with nonconvulsive status epilepticus. Some of the seizures were associated with minimal right facial twitching. At this time, her carbamazepine and divalproex sodium levels were 8.2 and 94 μg/ml, respectively. LEV tablets were added at 500 mg BID and the nonconvulsive status epilepticus resolved 36 h later. Within the next few days the patient returned to close to her pre-admission baseline. She was discharged on carbamazepine 600 mg BID, divalproex sodium 750 mg TID, lorazepam 0.5 mg BID, and LEV 500 mg BID. A few days later the LEV was increased to 1000 mg BID and over the following weeks to 2500 mg BID.

Discussion

In these six patients, LEV proved effective in several types of status epilepticus, including generalized, focal, and nonconvulsive status epilepticus. Etiologies included ischemic and hemorrhagic infarcts, static encephalopathy, CNS vasculitis, posttraumatic epilepsy, and noncompliance. All of these patients had been treated with at least two and as many as five AEDs prior to the addition of LEV. In all six cases, seizures terminated within 12—96 h of the first dose of LEV. No side effects attributable to LEV were observed. Expected side effects such as somnolence may not have been discernible due to the clinical setting that included multiple medications and postictal state (Table 1).

Another new AED, topiramate, has recently been reported to be effective in refractory status epilepticus.[11] Topiramate has multiple mechanisms of action including voltage-sensitive, use-dependent sodium channel blockade, similar to phenytoin.[11] The mechanism by which LEV exerts its antiepileptic effect is not known, but is likely different from topiramate. Recent investigations of LEV have demonstrated effects on N-type calcium channels[12] and reduction of potassium currents in hippocampal CA1 neurons.[13] How topiramate and LEV succeed in terminating status epilepticus remain under investigation.

Treatment of refractory status epilepticus typically requires intravenous pentobarbital, propofol, or midazolam, which may necessitate intubation and require vasopressor support. Oral AEDs such as topiramate or LEV have much to offer if they can pre-empt these more aggressive treatments. The lack of drug—drug interactions associated with LEV enhances its value in the setting of critically ill patients with status epilepticus. The new availability of a liquid LEV preparation and the development of an intravenous form will also facilitate treatment of this patient population.

Conclusions regarding LEV's effectiveness in controlling status epilepticus must be tempered by the

uncontrolled nature of these six cases. It may be that the patient's other AEDs finally took effect at the same time LEV was added, giving the appearance that LEV was responsible. Serum levels of LEV could have documented adequate absorption from the NG tube, and should be obtained in future studies. (In this observational study, clinical response was the treatment endpoint, and the practical value of serum LEV levels was limited due to their 1-week turn around time.) However, the promptness and consistency of the patients' response after addition of LEV favors a therapeutic action. (In Case #5, the patient responded after receiving LEV and lamotrigine together, making it difficult to discern whether it was the LEV or lamotrigine, or combination that resulted in seizure control).

As status epilepticus becomes more difficult to treat the longer it continues, one can only speculate whether LEV would have been more effective if used as initial treatment, rather than as adjunctive therapy late in the clinical course. These positive results combined with LEV's broad spectrum efficacy, favorable pharmacokinetics and side effect profile suggest that LEV may be beneficial as adjunctive treatment of status epilepticus. Randomized controlled trials of LEV as a treatment for status epilepticus should be considered.

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